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Intravenous and oral levetiracetam in patients with a suspected primary brain tumor and symptomatic seizures undergoing neurosurgery: the HELLO trial

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Abstract: BACKGROUND: Levetiracetam (LEV) is a newer anticonvulsant with a favorable safety profile. There seem to be no relevant drug interactions, and an intravenous formulation is available. Therefore, LEV might be a suitable drug for the perioperative anticonvulsive therapy of patients with suspected brain tumors undergoing neurosurgery. METHODS: In this prospective study (NCT00571155) patients with suspected primary brain tumors and tumor-related seizures were perioperatively treated with oral and intravenous LEV up to 4 weeks before and until 4 weeks after a planned neurosurgical procedure. FINDINGS: Thirty patients with brain tumor-related seizures and intended neurosurgery were included. Three patients did not undergo the scheduled surgery after enrollment, and two patients were lost to follow-up. Therefore, 25 patients were fully evaluable. After initiation of therapy with LEV, 100% of the patients were seizure-free in the pre-surgery phase (3 days up to 4 weeks before surgery), 88% in the 48 h post-surgery phase and 84% in the early follow-up phase (48 h to 4 weeks post surgery). Treatment failure even after dose escalation to 3,000 mg/day occurred in three patients. No serious adverse events related to the treatment with LEV occurred. CONCLUSION: Our data show the feasibility and safety of oral and intravenous LEV in the perioperative treatment of tumor-related seizures. Although this was a single arm study, the efficacy of LEV appears promising. Considering the side effects and interactions of other anticonvulsants, LEV seems to be a favorable option in the perioperative treatment of brain tumor-related seizures.

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Intravenous and oral levetiracetam in patients with a suspected primary brain tumor and symptomatic seizures undergoing neurosurgery: The HELLO trial.

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Running Title: Perioperative Levetiracetam in brain tumor patients

Clinical Trial Registration number: NCT00571155

Table 1. Patient characteristics

Age	years
Median	46
Range	23 - 78
Sex	% (n)
Female	26.7 (8)
Neurological status	% (n)
Abnormal	43.3 (13)
Tumor localization	% (n)
left hemisphere	73.3 (22)
frontal	46.7 (14)
temporal	26.7 (8)
parietal	13.3 (4)
occipital	3.3 (1)
more than one lobe	10.0 (3)
Tumor size	mm
Largest diameter, median	43
Range	11 - 72
No. of seizures (pre-study)	
Mean	4.8
Median	1
Range	1 - 61
Types of Seizures	% (n)
All	100.0 (139)
Simple partial seizures	76.3 (106)
Complex partial seizures	2.2 (3)
Generalized seizures	21.6 (30)
EEG results	% (n)
Focal slowing	73.3 (22)
Focal epileptiform discharges	3.3 (1)
Not done	3.3 (1)
Pre-Study Medication	% (n)
Levetiracetam	83.3 (25)
Carbamazepine [a]	6.7 (2)
Valproic Acid [a]	3.3 (1)
Other [a]	13.3 (4)
None	13.3 (4)
More than one	20.0 (6)
Steroid use	% (n)
Visit 1	30.0 (9/30)
Visit 2	35.3 (6/17)
Visit 3	74.1 (20/27)
Visit 4	29.2 (7/24)
Surgery	% (n)

Gross total resection,	16.7 (5)
Partial resection or extent of resection not validated by MRI	46.7 (14)
Stereotactic biopsy	26.7 (8)
No surgery	10.0 (3)
Histology (n=27)	% (n)
Glioblastoma	44.4 (12)
Anaplastic glioma	18.5 (5)
Low grade glioma [b]	18.5 (5)
Meningeoma	11.1 (3)
Metastasis	3.7 (1)
Abscess	3.7 (1)

[a] as per protocol AED other than LEV were withdrawn not later than 7 days before surgery
[b] including one papillary glioneural tumor

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Conflict of interest: Besides the funding of this trial none of the authors has to declare a conflict of interest.

SUMMARY

Background:

Levetiracetam (LEV) is a newer anticonvulsant with a favorable safety profile. There seem to be no relevant drug interactions, and an intravenous formulation is available. Therefore, LEV might be a suitable drug for the perioperative anticonvulsive therapy of patients with suspected brain tumors undergoing neurosurgery.

Methods:

In this prospective study (NCT00571155) patients with suspected primary brain tumors and tumor-related seizures were perioperatively treated with oral and intravenous LEV up to 4 weeks before and until 4 weeks after a planned neurosurgical procedure.

Findings:

30 patients with brain tumor-related seizures and intended neurosurgery were included. Three patients did not undergo the scheduled surgery after enrolment and two patients were lost for follow-up. Therefore, 25 patients were fully evaluable. After initiation of therapy with LEV 100 % of the patients were seizure-free in the pre-surgery phase (3 days up to 4 weeks before surgery), 88 % in the 48 h post-surgery phase and 84 % in the early follow-up phase (48 h to 4 weeks post surgery). Treatment failure even after dose escalation to 3000 mg/day occurred in 3 patients. No serious adverse events related to the treatment with LEV occurred.

Conclusion:

Our data show the feasibility and safety of oral and intravenous LEV in the perioperative treatment of tumor-related seizures. Although this was a single arm study, the efficacy of LEV appears promising. Considering the side effects and interactions of other anticonvulsants, LEV seems to be a favorable option in the perioperative treatment of brain tumor-related seizures.

INTRODUCTION

More than 40 % of all brain tumor patients develop symptomatic epilepsy during the course of their disease. In particular, seizures are a common presenting symptom that prompts diagnostic workup. Among primary brain tumors, the risk for seizures is higher for patients with low grade gliomas and with tumors located in the temporal lobe (5, 14, 29). In patients with brain metastasis seizures occur with a slightly lower incidence of 20-35%. Most patients with a suspected brain tumor then need to undergo a neurosurgical procedure, which is in itself associated with an increased risk of seizures. Thus, the control of seizures in the perioperative phase is an important goal in brain tumor management (4, 5, 11, 13, 20, 25, 29).

The pathomechanisms of seizures in brain tumor patients are incompletely understood. They occur because of local irritation due to the infiltrative tumor growth, but more specific mechanisms like disturbed peritumoral aminoacid distribution, altered local metabolism and pH, immunological factors and a perturbed distribution and function of glutamate receptors may also be involved (2, 19, 25).

According to current consensus, all patients with a brain tumor and a first seizure should be treated with antiepileptic drugs (AED). The efficacy of primary prophylactic treatment has not been demonstrated so far. Institutional standards for the treatment of patients with brain tumors and seizures often include treatment with phenytoin (PHT), carbamazepine (CBZ) or valproate (VPA). However, these AED have major side effects and can interact with accompanying medication or chemotherapy.

Several new AED are available that are devoid of clinically relevant drug interactions and do not influence hepatic metabolism. Therefore, although newer AED do not demonstrate a better efficacy, they are preferable for the treatment of brain tumor-related epilepsies (7, 24-26). One major disadvantage of most newer AED, however, is the lack of an intravenous formulation, that is necessary in emergency situations or in the perioperative phase. LEV was the first new AED with an intravenous formulation being available (1, 16, 17, 21). Therefore, LEV might be a first choice for the treatment of brain tumor-related epilepsy (3, 18, 23). Interest for LEV for perioperative treatment is therefore high although this is an off label use. However, only preliminary data from the study of Usery et al. are available that are based

on 17 patients (22). Therefore, we conducted a prospective registered clinical trial on oral and perioperative intravenous LEV in patients with a suspected primary brain tumor and symptomatic epilepsy at the time of initial diagnosis and before a scheduled neurosurgical intervention.

METHODS AND MATERIALS

Study population and study design

This trial included patients with a suspected primary brain tumor, with at least one tumor-related seizure and a planned neurosurgical procedure, i.e. resection or biopsy. This was an open-label, prospective, single-arm pilot study, which was performed at two German university hospitals. The study protocol and the patient consent form were approved by the Institutional Review Board and the German authorities (BfArM). The study was registered at www.clinicaltrials.gov (NCT00571155) and in the EudraCT database of the European Community (2007-005063-96). The study medication was provided by UCB Pharma (Belgium) and labeled according to legal guidelines.

Objectives

The primary objective was to evaluate whether a standardized pre-, peri-, and postoperative oral and intravenous LEV treatment of patients with brain tumor-related seizures is feasible. The secondary objectives were determination of safety, tolerability, efficacy and influence on quality of life.

Inclusion and exclusion criteria

Key patient inclusion criteria included: written informed consent, age > 18 years, suspected primary brain tumor on the basis of neuroradiological imaging (initial presentation), planned biopsy or cytoreductive surgery of the tumor, tumor-related, symptomatic epilepsy, Karnofsky performance score of at least 70 %, sufficient contraception for women before their menopause and adequate haematological, renal and hepatic function (white blood cell counts > $2*10^9$/l, hemoglobin > 10 g/dl, platelets > $100*10^9$/l, bilirubin <2*upper limit of normal range, aspartate aminotransferase and alanine aminotransferase < 3* upper limit of normal range, serum creatinine < 1,5 mg/dl). Exclusion criteria included: treatment with an antiepileptic drug other than LEV in the last seven days before surgery, known allergy against LEV or any of its components, other known severe side effects due to LEV, existing idiopathic or symptomatic epilepsy unrelated to the tumor, previous craniotomy or any other previous neurosurgical intervention, other severe co-morbidities, dementia or other clinically relevant changes in mental status, simultaneous

participation in another trial up to 28 days before inclusion, abuse of alcohol or other drugs, pregnancy or breast-feeding.

Treatment plan

The oral starting dose of LEV was 500 mg twice daily. After 72 hours the dose was escalated to 1000 mg twice daily. Because of the known dose response relationship for levetiracetam efficacy and the missing evidence for a dose response relationship for adverse events we chose this rather high dose for a patient population with a particular risk for further seizures (8). Only in the case of further seizures more than 24 hours after dose increase, the dose was escalated to 1250 mg twice daily and after 3 additional days to 1500 mg twice daily. On the day of surgery, patients received an oral dose of LEV in the morning. In the evening of the day of surgery, patients received LEV as an intravenous infusion at the same dose as the last oral dose. The intravenous application was scheduled for 36 hours or until oral application was possible again. The following oral dose was equal to the last intravenous dose. If a seizure occurred more than 72 hours after surgery at a dose of 2000 mg/day, dose escalation was performed as described above. Seizures during the first 72 hours after surgery did not mandate a dose escalation. If further seizures occurred after dose escalation to 3000 mg/day, study participation was discontinued.

After the end of the regular study participation 4 weeks after surgery the anticonvulsive medication was solely at the discretion of the treating physician.

Stopping criteria

Treatment failure was defined as (i) at least one further seizure occurring at the 3000 mg/day dose level or (ii) the necessity to introduce another AED. Transient treatment with benzodiazepines was allowed. Study participation was also discontinued if a second surgery became necessary, if a patient withdrew his informed consent, if there was a significant deterioration of the general condition or a WHO toxicity of grade 4, which could not be explained by anything else but LEV.

Patient monitoring

To ensure a close monitoring of the study participants, four study visits were scheduled during the study. The first visit was done on the day of inclusion, 3 days to 4 weeks before surgery. The second visit was

due 1 to 7 days before surgery. The third and fourth visits were done 2 to 7 days and 28 to 35 days after surgery, respectively. Data collected included medical history, history of seizures, EEG, tumor status, Karnofsky performance status, mini-mental status, quality of life questionnaire, neurological examination, vital signs, laboratory parameters, adverse events and medication.

EEG

The EEG analysis was done at study enrolment and at visit 4 by an independent, experienced neurologist. The neurologist first indicated whether the EEG was normal or pathologic. Second, he or she marked if there was a diffuse abnormally slow rhythm, a focal increase of slow frequency rhythms, or focal or generalized epileptiform discharges. It was at the discretion of the neurologist to rate the follow-up EEG compared to the baseline EEG as unchanged, better or worsened.

RESULTS

Patients

As per protocol, 30 patients were enrolled from January 2008 to June 2009 at two German university hospitals. Due to unexpected changes in an additional preoperative MRI, three of these patients did not undergo the scheduled neurosurgical intervention. Two patients were lost for follow-up. Therefore, 25 patients were fully evaluable. The characteristics of all included patients (n=30) are shown in Table 1. A somewhat lower percentage of female participants and a higher rate of left sided tumors are notable.

Seizure history, baseline EEG results, pre-study medication and steroid use are also shown in Table 1. Of all included patients, 16 (53.3%) had only one seizure before inclusion, 6 patients (20.0%) had two seizures and 5 patients (16.7%) hade more than 4 seizures. Of note, 83.3% of all included patients were already treated with LEV before inclusion in this study, anticipating subsequent study enrolment. In median LEV was started 19 days before surgery. As expected, steroid use was quite common in this study population. At the time of study enrollment 30.0% of all patients already were on steroids. This figure increased up to 74.1% at visit 3, but came back to 29.2% at the end of the study period.

The type of surgery and the neuropathological findings are shown in the lower part of Table 1. A postoperative MRI scan within 72 h was done in 12 patients, whereas 10 patients were postoperatively examined by computed tomography only, e.g., after stereotactic biopsy. In 3 patients, no early postoperative scan was acquired. In 22 of the 27 patients that underwent surgery, a neuropathological diagnosis of a primary intrinsic brain tumor was made. In the remaining 5 patients, meningeoma (n=3), brain metastasis (n=1) or abscess (n=1) were found.

A follow-up EEG was available in 26 patients. Of these, 6 (23.1%) showed improvement, 17 (65.4%) were unchanged and 3 (11.5%) had a worsened result compared to the baseline EEG at study enrolment. Of the fully evaluable patients, 23 completed the quality of life questionnaire (EORTC QLQ-C30) at baseline and at the end of the study. The results on overall health (question 29) and overall quality of life (question 30) are shown in figure 1. There were no detectable differences between study inclusion and

end of the study. Mini Mental Status Test results at the 3 follow-up visits did not differ from visit 1 (Figure 1).

Primary objective

The feasibility of the standardized oral and intravenous treatment regimen with LEV was excellent. Of the fully evaluable patients only one patient did erroneously not receive the scheduled intravenous treatment, because the patient was able to swallow LEV tablets soon after surgery. All other patients received intravenous LEV for up to 36 hours. Regarding the oral treatment, it is notable, that three patients received merchandised LEV (Keppra®) instead of study medication during their study participation. However, since LEV is licensed for the monotherapy treatment of focal epilepsy, this was not regarded as a severe violation of the treatment regimen as prespecified in the study protocol.

Secondary objectives

Safety and tolerability of LEV were very good in this study. During the whole study period, 3 severe adverse events (SAEs) and 4 adverse events (AEs) were registered. One patient died 5 weeks after surgery from pulmonary embolism. Another patient was hospitalized because of a suspected recurrence of the initial intracranial abscess (Table 1). The third patient was admitted to hospital during study participation because of a generalized seizure. Four days later this patient was excluded from the study because a second surgery was necessary. Taken together, none of the three SAEs had a relationship to the study medication. Four AEs in three patients occurred during the study period. One patient suffered a mild epidural hematoma without the need for specific therapy. Another patient had an AE with paresthesia and a visual field deficit. The last patient had two AEs, one regarding paresthesia and one regarding a nystagmus and a mild disturbance of memory. The AEs in these two patients were considered to be potentially attributable to the study drug.

Efficacy was measured as the number of patients with seizures during the different study periods (Figure 1). By definition this number for the pre study period was 25 (fully evaluable patients), because at least one tumor-related seizure was an inclusion criterion. During the pre surgery period (study enrolment until surgery), which was a minimum of 3 days up to a maximum of 4 weeks, no seizures occurred in any

patient. In the 48 hours post surgery period 3 of the 25 fully evaluable patients suffered at least one seizure, therefore the seizure-free rate in this period was 88.0%. In the post surgery period, 4 patients had further seizures, resulting in a seizure-free rate of 84.0%. Seizures during the 48 hours post surgery period were generally treated with benzodiazepines only and did not mandate dose escalation of LEV. Overall, six patients had seizures during this study while on LEV therapy, as one patient had seizures during the 48 hours post surgery period and the post surgery period. Compared to the characteristics of the whole cohort, a rather high number of patients with a biopsy is noteworthy (4 out of 6 patients, 66.7%). In contrast, only 8 patients (26.7%) of the 30 included patients had a biopsy, resulting in a 50% postoperative seizure rate in this subgroup. 11 of all included patients (36.7%) compared to 4 of the 6 patients (66.7%) with seizures during the study participation presented with generalized epilepsy before study inclusion. Therefore, patients with generalized epilepsy, as well as patients only having a biopsy, might have a higher risk for postoperative seizures even under anticonvulsive treatment with LEV.

Two of these 6 patients had seizures during the 72h postoperative period. One patient received a single dose of benzodiazepines, while the other had two short self-limiting seizures that were not treated. In both cases, no dose escalation of LEV was administered. A third patient suffered one seizure in the 4 weeks postoperative period resulting in a dose escalation of LEV to 3000mg per day according to the study protocol. Treatment failure occurred in three patients. One patient had 3 seizures in the direct postoperative phase requiring a PHT rescue medication. Another patient had two seizures in the 48h post-surgery phase, therefore LEV was increased to 4000mg per day. However, this patient subsequently suffered 5 additional seizures in the 4 weeks post-surgery period, received multiple doses of benzodiazepines and finally VPA rescue medication. The third patient had a single seizure during the 4 weeks post-surgery period. He was put on a continuous benzodiazepine schedule and had a second surgery, two reasons for his study discontinuation.

The study participation ended 4 to 5 weeks after the neurosurgical intervention. However, we followed the patients for another 6 months post study participation. As this was a retrospective analysis the available information on the post study period is limited. From the 25 initially evaluable patients, 21

could be questioned for seizure control and medication. Of these patients, 8 had at least one further seizure, resulting in a dose escalation of LEV in 5 and in add-on therapy with another AED in 3 cases. Of these 8 patients 4 had the diagnosis of a glioblastoma, 2 had a anaplastic glioma, one had a low-grade oligoastrocytoma and one had a brain metastasis. One patient stopped levetiracetam medication resulting in a seizure and 4 showed a progressive tumor on the following MRI scans. On the remaining 3 patients no detailed follow-up information were available.

DISCUSSION

To date, there are no established guidelines regarding anticonvulsant therapy in patients with newly diagnosed brain tumors and seizures. However, both seizures and conventional AED may cause relevant morbidity or interfere with brain tumor therapy.

LEV is a newer AED with several advantages over conventional AED. It has a favorable pharmacological and pharmacokinetic profile, has no effects on liver enzymes and no known relevant drug interactions. Its side effects are generally mild and, since 2006, an intravenous formulation is available. LEV has proven efficacy in monotherapy of focal epilepsies or as add-on therapy in idiopathic and symptomatic epilepsies. However, data on LEV for brain tumor-related seizures, especially at the time of initial diagnosis and during the neurosurgical intervention, are rare. We hypothesize that LEV could be a suitable drug (off-label use) for the treatment of brain tumor related seizures in the perioperative period. Therefore, we conducted the first registered prospective trial of oral and intravenous LEV in patients with a suspected primary brain tumor and symptomatic epilepsy undergoing neurosurgery.

According to protocol, 30 patients were enrolled during an 18 month period, with 25 patients being fully evaluable. The rather high proportion of partial resections and biopsies in our series may be due to a high percentage of left sided and suspected low-grade tumors.

The feasibility of a standardized oral and intravenous treatment with LEV in this two center study was good. The treatment regimen corresponding to the study protocol was effortlessly realized in daily practice.

Safety and tolerability of oral and intravenous LEV were excellent in this defined patient population and treatment setting. No LEV-related SAE occurred during the whole study period. We did not observe agitation or psychoses as known LEV-related side effects in our patients. This might be due to the short study duration or the low number of patients, since both side effects occur in less than 10% of patients treated with levetiracetam for longer periods. Additionally, there was no decline in overall quality of life, overall health or cognitive function, as assessed by EORTC quality of life questionnaire and MMST (Figure 1). This corroborates the recent results on safety and tolerability from retrospective or smaller

studies applying LEV in brain tumor patients or in patients undergoing any supratentorial neurosurgery (6, 9, 10, 18, 22, 23, 30).

Regarding efficacy we found encouraging seizure-free rates during the different study periods in this patient population with a high risk of seizures. We consider the seizure-free rate of 84% in the 4 weeks post surgery phase excluding the 48 hours after surgery the most relevant finding. Treatment failure occurred in only three patients who needed an add-on therapy with a second AED and were therefore excluded from study. In the retrospective analysis of the 6 months follow-up, an add-on therapy was necessary in another 3 out of 21 patients, whereas 5 patients had a dose escalation of LEV. These results confirm and expand the data of a prematurely discontinued similar trial (22). Brain tumor patients with seizures were perioperatively treated with levetiracetam and the authors report on a seizure control rate of 94.1 % (in hospital follow-up) and 91.7 % (post-discharge follow-up). Seizure control was defined as a reduction in seizure activity of at least 50 %. Another comparable study is the retrospective analysis of Merrel and colleagues (9). They analyzed 76 patients, 25 treated with phenytoin and 51 with levetiracetam. 5 (7.8 %) of the 64 patients having had a seizure prior to surgery suffered a seizure during the 30 day postoperative period. Two of these patients were being treated with levetiracetam and 3 with phenytoin. Twelve patients (16%) were not taking an AED during the 30-day postoperative period. Two (17%) experienced their index seizure in this interval. In summary, the seizure rate in the perioperative period in patients with preoperative seizures and anticonvulsive treatment might be around 10 %. The seizure rate in the same population without treatment at least seems to be above 20 %.

Our study tested a novel strategy for an important clinical constellation. For the decision which AED to use in this situation one needs to take into account all the pros and cons of the available AED. There are several known interactions with the planned surgery, the possibly required radiotherapy and chemotherapy. VPA, for example, potentially impairs platelet function and coagulation, thus making it unattractive for the application during a neurosurgical intervention or adjuvant chemotherapy. A prospective monotherapy study by Nasreddine and Beydoun in 265 patients showed that 17.7% of these patients experienced at least one episode of thrombocytopenia (platelet counts $\leq$ 100,000/µl) (12).

Enzyme-inducing AED (EIAED) like PHT or CBZ can decrease plasma levels of chemotherapeutic drugs, e.g. irinotecan and paclitaxel, or steroids via induction of liver enzymes (mainly CYP3A4). VPA, in contrast, is an inhibitor of cytochrome P450 isoenzymes and the concentration of several chemotherapeutic drugs, e.g. nitrosureas and etoposide, can be increased due to reduced elimination (15, 27, 28). The metabolism of small molecule kinase inhibitors is also frequently influenced by EIAED and VPA. Older AED in general are thought to have side effects on cognitive function, which is especially important for patients who already may suffer from tumor-related cognitive decline and who have to undergo a radiotherapy possibly resulting in further cognitive impairment. The dimension of the problems that interactions of older AED cause is illustrated by the analysis of Usery et al., who identified 92 avoided potential drug interactions in a very similar patient cohort (n=17), many with potentially serious consequences (22).

In conclusion, our data show the feasibility and safety of oral and intravenous LEV in the perioperative treatment of tumor-related seizures. Although this was a single arm study, the efficacy of LEV appears promising. Considering the side effects and interactions of other anticonvulsants, LEV seems to be a favorable option in the perioperative treatment of brain tumor-related seizures.

DISCLOSURE

Part of this study was sponsored by an unrestricted grant of the UCB Pharma GmbH to M.W. and J.P.S..

Besides the funding of this trial none of the authors has to declare a conflict of interest.

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O.B. and M.H. contributed equally to this work.

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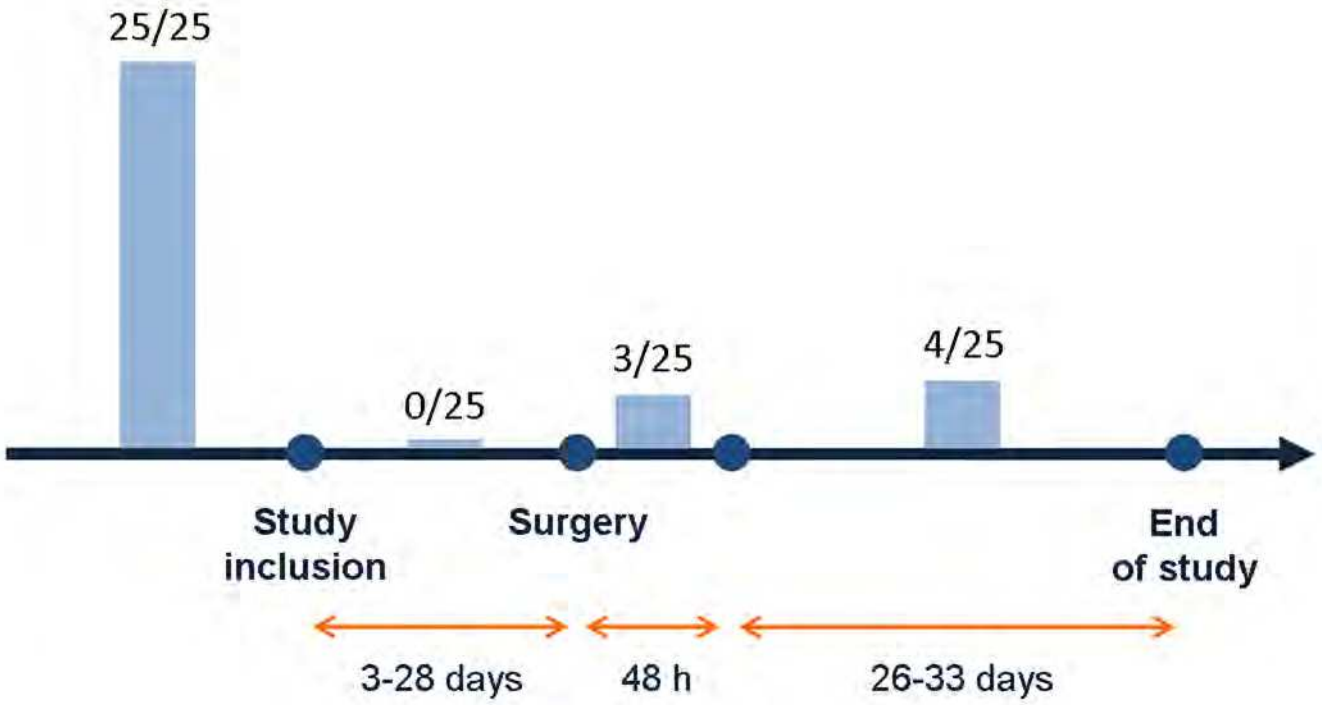
CAPTIONS

Figure 1. Efficacy of treatment with levetiracetam (patients with seizures) and influence on Mini Mental Status (MMS), Overall Quality of Life (QoL) and Overall Health Status (GHS) during the four study phases.

Table 1. Characteristics of the included patients.



MMS (median)	29	29	29	29
QoL (mean)	4.47+/-1.87	n.d.	n.d.	4.46+/-1.36
GHS(mean)	4.23+/-1.63	n.d.	n.d.	4.96+/-1.48

Table 1. Patient characteristics

Age	years
Median	46
Range	23 - 78
Sex	% (n)
Female	26.7 (8)
Neurological status	% (n)
Abnormal	43.3 (13)
Tumor localization	% (n)
left hemisphere	73.3 (22)
frontal	46.7 (14)
temporal	26.7 (8)
parietal	13.3 (4)
occipital	3.3 (1)
more than one lobe	10.0 (3)
Tumor size	mm
Largest diameter, median	43
Range	11 - 72
No. of seizures (pre-study)	
Mean	4.8
Median	1
Range	1 - 61
Types of Seizures	% (n)
All	100.0 (139)
Simple partial seizures	76.3 (106)
Complex partial seizures	2.2 (3)
Generalized seizures	21.6 (30)
EEG results	% (n)
Focal slowing	73.3 (22)
Focal epileptiform discharges	3.3 (1)
Not done	3.3 (1)
Pre-Study Medication	% (n)
Levetiracetam	83.3 (25)
Carbamazepine [a]	6.7 (2)
Valproic Acid [a]	3.3 (1)
Other [a]	13.3 (4)
None	13.3 (4)
More than one	20.0 (6)
Steroid use	% (n)
Visit 1	30.0 (9/30)
Visit 2	35.3 (6/17)
Visit 3	74.1 (20/27)
Visit 4	29.2 (7/24)
Surgery	% (n)

Gross total resection,	16.7 (5)
Partial resection or extent of resection not validated by MRI	46.7 (14)
Stereotactic biopsy	26.7 (8)
No surgery	10.0 (3)
Histology (n=27)	% (n)
Glioblastoma	44.4 (12)
Anaplastic glioma	18.5 (5)
Low grade glioma [b]	18.5 (5)
Meningeoma	11.1 (3)
Metastasis	3.7 (1)
Abscess	3.7 (1)

[a] as per protocol AED other than LEV were withdrawn not later than 7 days before surgery
[b] including one papillary glioneural tumor